Reprinted from MEDICAL ANNALS OF THE DISTRICT OF COLUMBIA
Vol. XXVIII, No. 8, August, 1959
Printed in U.S.A.

CLINICAL TRIAL OF GUANETHIDINE, A NEW TYPE OF ANTIHYPERTENSIVE AGENT*†

EDWARD D. FROHLICH, M.D.

Fellow in Cardiovascular Research, Department of Medicine, Georgetown University School of Medicine

EDWARD D. FREIS, M.D.

Chief of Medical Service, Veterans Administration (Mt. Alto) Hospital; Associate Professor of Medicine, Georgetown University School of Medicine

MAXWELL and his associates[1, 2] recently found in dogs that hexahydro-1-azepinepropionamidoxime dihydrochloride (SU-4029) lowered the blood pressure of neurogenic and renal hypertensive dogs, blocked the carotid occlusion pressor reflex, and eliminated the hypertension elicited by amphetamine and ephedrine but enhanced the pressor responses to norepinephrine and epinephrine. Similar effects also were observed with the use of SU-5864 [2-(octahydro-1-azocinyl)-ethyl] guanidine sulfate.[3] Maxwell et al postulated that these drugs had a novel mode of action characterized by inhibition of efferent sympathetic nerve activity at an unknown peripheral site. This preliminary report describes the clinical effects of SU-5864 (guanethidine) in hypertensive patients.

MATERIALS AND METHODS

Fifteen male patients were selected from the hypertensive clinic, and all antihypertensive drugs were discontinued for a period of 2 weeks. Following this control period SU-5864 was administered in an oral dose of 50 mg. once daily in the morning. The dosage was increased or decreased from that level depending on the patient's response. Patients were seen at least once weekly and their blood pressures determined in the supine, sitting and erect positions after 15 minutes' rest. Approximately half of the patients recorded their blood pressure at home. The blood urea nitrogen and blood hemoglobin concentrations as well as the white blood count were determined prior to and at the conclusion of the study.

* From the Veterans Administration Hospital; the Department of Medicine, Georgetown University School of Medicine; and the Cardiovascular Research Laboratory, Georgetown University Hospital, Washington 7, D. C.

† Supported in part by the United States Public Health Service Grant H-720 (National Heart Institute).

Results

Antihypertensive effects. SU-5864 produced primarily an orthostatic hypotension (table 1). The reductions of systolic and diastolic pressures averaged 7/4 per cent in the supine position, 18/14 per cent in the sitting posture, and 27/26 per cent in the erect position. There was considerable variation in different patients, however, so that a few exhibited significant reductions in supine blood pressure (table 1) while others showed no change or slight increases of blood pressure in the supine position. Some patients who recorded the blood pressure at home noted diurnal fluctuations with low orthostatic levels on arising which rose progressively during the day. No evidence of tolerance or resistance to the antihypertensive effect was noted during the 4 to 9 weeks (mean 6 weeks) of treatment.

Dose response pattern. Effective maintenance dosage varied widely from 12.5 to 150 mg. (average 50 mg.) per day. Antihypertensive activity usually appeared 24 hours after an

TABLE 1

Clinical Effects of SU-5864 in Fifteen Hypertensive Patients

Patient	Age	Race	Grade	Blood Pressure Untreated (mm. Hg Sitting*)	Dose (mg./d.)	Duration of Treatment (Weeks)	Blood Pressure on Treatment (mm. Hg)			Change‡ (mm. Hg)			Heart Rate on Treatment (per minute)			Side-effects
							Supine	Sitting	Erect	Supine*	Sitting	Erect*	Supine	Sitting	Erect	
A. H.	64	N	3	260/130	12.5	5	210/105	185/95	160/90	50/20	75/35	90/40				Orthostatic faintness
W. E.	49	N	2	200/130	12.5	8	150/112	140/110	130/90	50/18	60/20	60/45	52	56	68	Nasal stuffiness
J. W.	52	N	2	180/140	75	8	170/130	138/108	110/88	10/0	42/32	70/52	58	62	76	Nasal stuffiness
R. J.	45	N	3	185/130	25	8	155/120	155/108	130/98	30/10	30/22	50/37	56	68	84	Fatigue, weakness
H. F.†	38	N	2	126/96	50	6	138/96	122/90	110/82	+8/+6	4/6	16/18	60	62	64	None
A. J.	48	N	2	160/100	50	5	140/110	128/98	98/72	+20/+10	32/2	62/28	50	58	76	Weakness, impotence
J. P.	57	N	2	180/120	150	5	210/130	180/118	150/108	+30/+15	0/2	30/12	44	52	60	Nasal stuffiness
W. B.	68	N	2	180/120	25	6	190/126	130/102	100/80	+10/+6	50/18	80/50	64	76	82	Drooping eyelids
L. M.	53	N	1	205/120	62.5	6	200/130	185/120	155/105	5/+10	20/0	45/20	56	60	62	Drooping eyelids, blurred vision
S. S.	65	W	1	180/110	50	4	170/100	160/100	135/80	10/10	20/10	45/30	52	76	76	Weakness, impotence
N. B.	52	N	2	175/98	50	4	170/100	130/100	135/80	10/+5	15/+2	40/18	72	80	80	Diarrhea
E. G.	46	N	2	190/130	100	4	190/110	180/108	158/90	0/20	10/22	32/40	68	72	76	Diarrhea, weakness, impotence
S. B.	49	N	2	220/130	12.5	7	190/110	135/90	112/70	30/20	85/40	78/70	50	58	64	Orthostatic faintness, diarrhea, blurred vision
W. E.	37	N	1	210/120	50	4	175/112	140/100	145/100	38/8	70/20	65/20	60	68	68	None
W. D.	28	W	1	150/110	75	9	170/120	155/120	150/120	+20/+10	+5/+10	+10/+5	52	64	64	Impotence, orthostatic syncope, diarrhea, blurred vision
Mean	50			187/118	50	6				12/4	34/14.5	50/32	57	65	71	

* Although not reported because of minimal differences from sitting B.P. the control supine and erect pressures were used in calculating B.P. changes after treatment.

† Sympathectomy—transthoracic 8 years ago.

‡ Reduction in blood pressure unless otherwise indicated.

effective dose level and often progressed over the succeeding 2 or 3 days. Because of this cumulative effect severe orthostatic hypotension and other side-effects such as diarrhea could be precipitated by raising the dosages too rapidly. The duration of the orthostatic antihypertensive effect lasted as long as 4 days to 1 week after discontinuation of oral dosage. This was observed when drug administration was stopped because of severe postural hypotension or other side-effects. The prolonged duration of action probably contributed to the cumulative action of SU-5864.

Bradycardic effect. Unlike the adrenergic blocking agents, SU-5864 produced a decrease in heart rate to an average level of 57 (range 44 to 68) beats per minute with the patient in the supine position. Reflex increase in heart rate was not blocked, however, since the average rate increased to 65 in the sitting posture and 71 beats per minute in the erect position (table 1).

Side-effects. In addition to the bradycardia certain other side-effects suggested parasympathetic stimulation or at least parasympathetic effects unopposed by sympathetic activity. These side-effects included nasal stuffiness in 3 patients, drooping of the upper eyelids in 2, and diarrhea in 5. The diarrhea was severe and accompanied by abdominal cramps in 3 of these cases. It was readily controlled by methantheine bromide (Banthine), 50 to 100 mg. once or twice daily.

Four patients complained of impotence. Unlike the impotence experienced after ganglionic blocking agents, libido and ability to obtain an erection were not impaired. However, ejaculation could not be consummated, a reaction similar to the sexual impairment caused by lumbar sympathectomy. Orthostatic weakness and faintness were experienced regularly when the dosage was increased beyond tolerable limits, and 1 patient developed syncope. Dosage manipulation was necessary to achieve the optimal degree of orthostatic hypotension. Several patients complained of mild intermittent blurring of vision, although their pupils were neither dilated nor unresponsive to light or accommodation. This complaint disappeared in all patients after several weeks of treatment. No significant changes were noted in the hemogram or the blood urea nitrogen level.

Discussion

The presence of orthostatic hypotension and failure of ejaculation suggest a specific sympathetic blocking action of SU-5864 consistent with the pharmacologic studies in animals.[3] The presence of diarrhea and bradycardia, and the absence of dryness of the mouth or disturbance in pupillary accommodation indicate that the parasympathetic nervous system is not inhibited. The absence of tachycardia is inconsistent with the action of adrenergic blocking drugs such as tolazoline or dibenzyline.

The ability of SU-5864 to produce an orthostatic hypotension comparable to that achieved with the ganglionic blocking drugs but without the side-effects of parasympathetic inhibition makes this agent worthy of further study. The diarrhea produced by SU-5864 could be controlled with parasympathetic blocking drugs. The disturbance of sexual function is less complete and, therefore, less objectionable to the patients than that produced by ganglionic blockade. The disadvantages of SU-5864 include the predominantly orthostatic antihypertensive effect leading to postural faintness and even syncope, and the necessity for critical dosage adjustment. These disadvantages are similar to those experienced with the ganglionic blocking drugs. The prolonged duration of action of SU-5864 is an additional inconvenience and possible potential danger, since severe orthostatic hypotension may persist for several days after the drug has been withdrawn.

Preliminary clinical evidence suggests that the following measures may facilitate treatment with this agent: (1) gradual increase in dosages beginning at a level of 12.5 mg. once daily for

the first week and increasing by increments of 12.5 mg. at weekly intervals, and (2) daily home blood-pressure recordings taken with the patient in the erect position and with instructions that the patient discontinue the medication if the blood pressure falls below a given level. Preliminary evidence suggests that administration of chlorothiazide as an adjunct seems to dampen out the wide diurnal swings of blood pressure seen in some of the patients. SU-5864 probably should be restricted to the more severe and resistant cases in which the blood pressures are not controlled with chlorothiazide alone or chlorothiazide with small doses of hydralazine and/or reserpine. Although no serious toxic effects have yet appeared following SU-5864, it is still too early to be certain that they will not occur with further exhibition of the drug.

Summary

Guanethidine, a new type of sympathetic nervous system inhibitor, was given orally in single daily dosages to 15 hypertensive patients for periods varying from 4 to 9 weeks. The average effective dose was 50 mg. per day (range 12.5 effective dose was 50 mg. per day (range 12.5 to 150 mg.). The response was characterized by a potent, orthostatic, antihypertensive effect similar to that seen with the ganglionic blocking drugs but without the side-effects of parasympathetic blockade. However, some of the difficulties associated with ganglionic blocking drugs such as the need for careful dosage adjustment also characterized SU-5864 and were even aggravated by the prolonged duration of action of the drug. Side-effects included diarrhea, failure of ejaculation, and bradycardia.

BIBLIOGRAPHY

1. Maxwell, R. A., Ross, S. D., and Plummer, A. J.: Pharmacology of hexahydro-1-azepinepropionamidoxime dihydrochloride (SU-4029). J. Pharmacol. & Exper. Therap., 1958, **123,** 128.
2. Maxwell, R. A., and others: Concerning the mechanisms of the cardiovascular actions of hexahydro-1-azepinepropionamidoxime (SU-4029). Ibid., 1958, **124,** 127.
3. Maxwell, R. A., Mull, R. P., and Plummer, A. J.: [2-(Octahydro-1-azocinyl)-ethyl]-guanidine sulfate (SU-5864), a new synthetic antihypertensive agent. Experientia, in press.